Population-adjusted treatment comparisons

Estimates based on MAIC and STC

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NICE DSU TECHNICAL SUPPORT DOCUMENT 18: METHODS FOR POPULATION-ADJUSTED INDIRECT COMPARISONS IN SUBMISSIONS TO NICE

REPORT BY THE DECISION SUPPORT UNIT

December 2016

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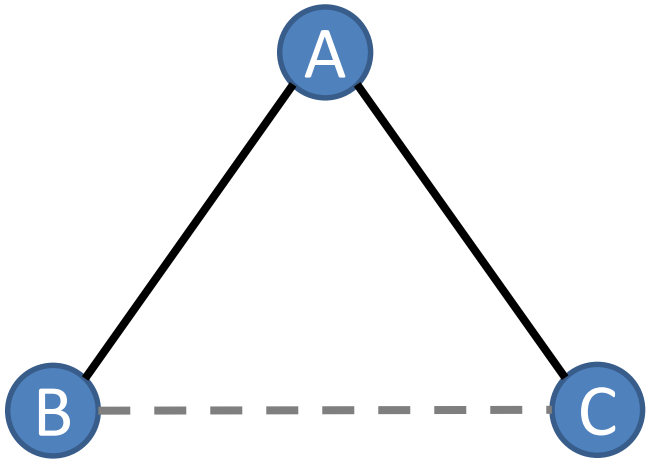
Outline

- Background
  - Standard indirect comparisons
  - Population adjustment
- Matching-Adjusted Indirect Comparison (MAIC) and Simulated Treatment Comparison (STC)
- Assumptions and properties
- Recommendations

Background: Indirect Comparisons

Wish to compare two treatments B and C

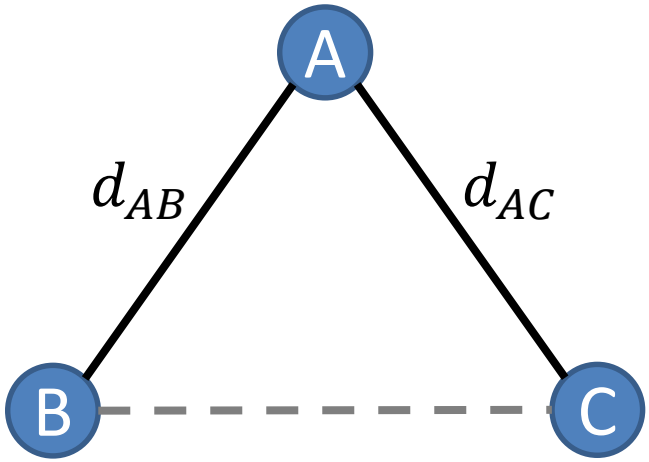
- Not studied in the same trial
- Instead, each compared with a common comparator A through AB and AC trials.



Background: Indirect Comparisons

Standard indirect comparisons:

- $d_{BC} = d_{AC} - d_{AB}$
- Biased if there are imbalances in effect modifiers *(EMs)* between AB and AC; $d_{AB(AB)} \neq d_{AB(AC)}$



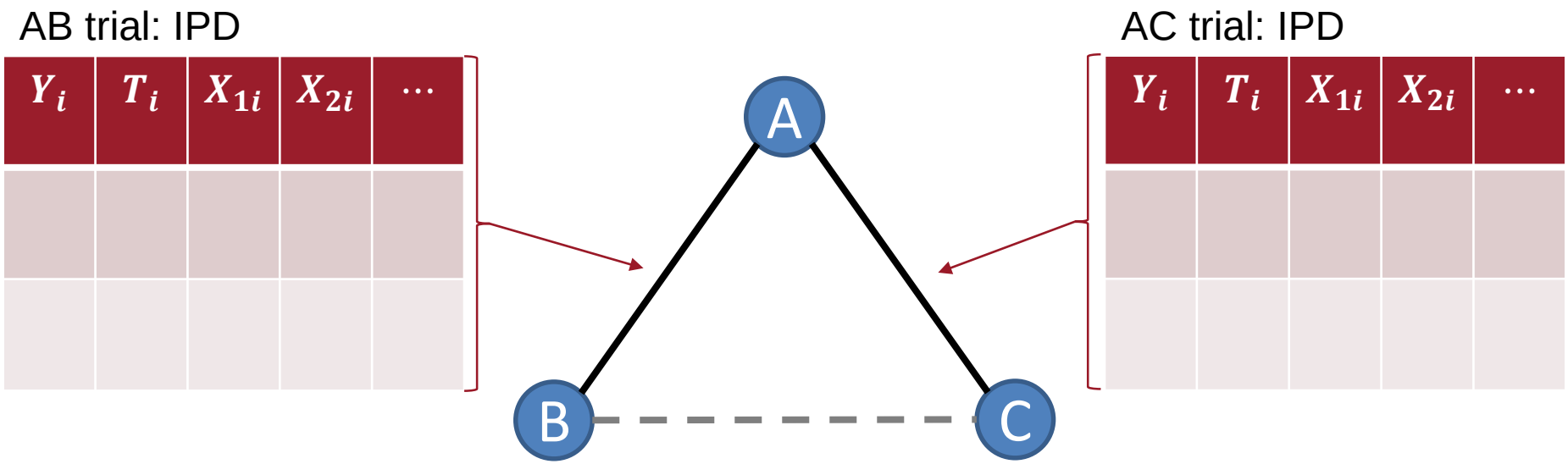
Background: Population Adjustment

- Standard indirect comparisons assume constancy of relative effects
- Population adjustment methods seek to adjust for imbalance in EMs
  - Relaxed constancy assumption
  - Create a fair comparison in a specific target population

Background

Ideal scenario: full individual patient data (IPD)

- "Gold standard" – IPD meta-regression



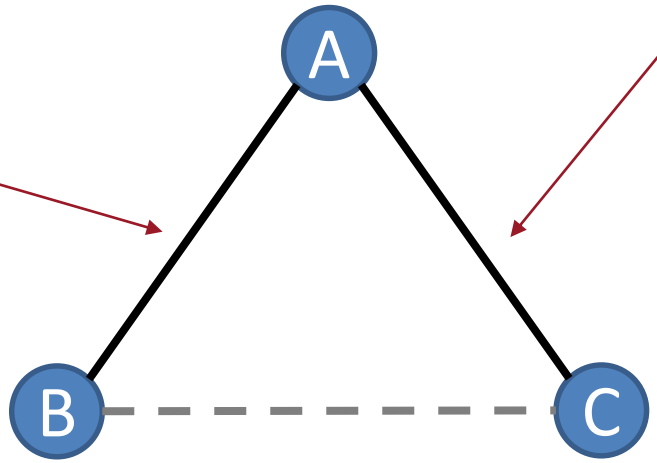
Background

Common scenario: limited IPD

- Several recent methods make use of mixed data

AB trial: IPD

Y_i	T_i	X_{1i}	X_{2i}	⋯



AC trial: aggregate data

$\bar{Y}_A, \bar{Y}_C, \bar{X}_1, \bar{X}_2, \ldots$

$\sigma_A, \sigma_C, f_{\boldsymbol{X}}(\cdot)$

Population adjustment: MAIC and STC

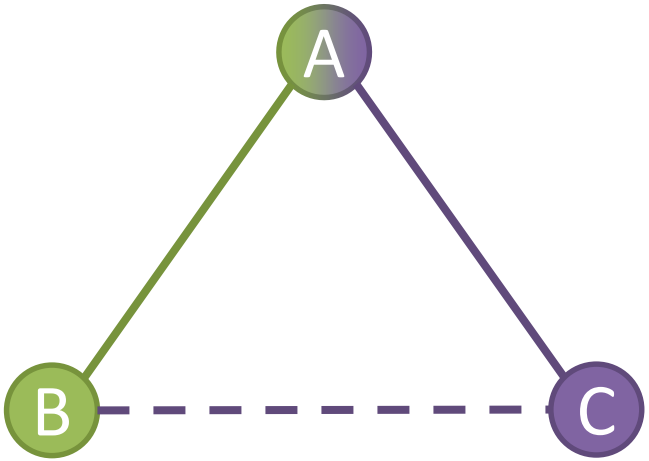
Matching-Adjusted Indirect Comparison	**Simulated Treatment Comparison**
• Population reweighting method	• Outcome regression method
• Weight AB individuals to balance covariate distribution with AC trial	• Fit regression model in AB trial
• Estimate outcomes on A and B in AC trial using weights	• Estimate outcomes on A and B in AC trial using regression model
• Check distribution of weights, effective sample size	• Standard model checking, AIC/DIC, examine residuals…

- AB and AC population must have sufficient overlap
  - Compare covariate distributions, inclusion/exclusion criteria
- Not the only approaches, but at present the most popular

Population adjustment

Two possible forms of indirect comparison

Anchored



Unanchored

Population adjustment

Two possible forms of indirect comparison

Anchored

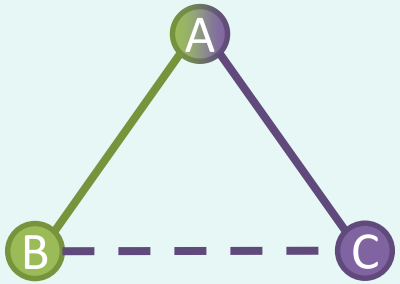
$$\hat{\Delta}_{BC(AC)} = g\left(\bar{Y}_{C(AC)}\right) - g\left(\bar{Y}_{A(AC)}\right) - \left(g\left(\hat{Y}_{B(AC)}\right) - g\left(\hat{Y}_{A(AC)}\right)\right)$$

Unanchored

$$\hat{\Delta}_{BC(AC)} = g\left(\bar{Y}_{C(AC)}\right) - g\left(\hat{Y}_{B(AC)}\right)$$

- Comparison is on a given transformed scale
- The latter requires much stronger assumptions, but doesn't need a common comparator arm

Assumptions and properties: constancy

	Anchored		Unanchored
			
Form of comparison	Standard indirect comparison	Anchored population-adjusted indirect comparison	Unanchored population-adjusted indirect comparison
Constancy assumption	Constancy of relative effects $d_{AB(AB)} = d_{AB(AC)}$	Conditional constancy of relative effects Predict $d_{AB(AC)}$ from *AB* trial	Conditional constancy of absolute effects Predict $Y_{B(C)}$ from *B* trial
Valid only if	No effect modifiers in imbalance	All effect modifiers known and adjusted for	All effect modifiers and prognostic variables known and adjusted for
Data	Only requires aggregate data	Requires IPD on at least one trial	Requires IPD on at least one trial

Assumptions and properties

Other assumptions:

- Studies are internally valid
- Lack of joint distribution leads to additional assumptions about correlations between covariates

Assumptions and properties

Both MAIC and STC produce estimates of relative treatment effect that are specific to the AC population

- This is unlikely to be representative of the decision target population
- If so, population-adjusted estimates are irrelevant for the decision…
- Can make use of the shared EM assumption, if justified
- Further research ongoing

Recommendations

Motivation of the recommendations

- Reproducibility, consistency, transparency
- Minimising bias and maximising precision

Recommendations

1. Anchored comparisons are always preferred to unanchored comparisons
2. Anchored comparisons should be justified with evidence for effect modification prior to analysis
3. Unanchored comparisons should show that absolute outcomes can be accurately predicted, estimate likely range of residual bias

Recommendations

4. Anchored analyses need only adjust for EMs. Unanchored analyses must adjust for all EMs and prognostic variables.
5. Comparison should be made on the linear predictor scale
6. Target population must be clearly specified, estimates generated for this population

Reporting guidelines and example R code available online

Thank you

NICE National Institute for Health and Care Excellence

The TSD was commissioned and funded by the Decision Support Unit at the National Institute for Health and Care Excellence.

MRC Medical Research Council

Ongoing work is supported by the Medical Research Council grant number MR/P015298/1.

Phillippo, D.M., Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE.* 2016. Available from http://www.nicedsu.org.uk

Phillippo, D.M., Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. *Methods for population-adjusted indirect comparisons in health technology appraisal.* In press. Medical Decision Making.